



Glaisyer, E. L., Watt, M. S., & Booker-Milburn, K. I. (2018). Pd(II)-Catalyzed [4 + 2] Heterocyclization Sequence for Polyheterocycle Generation. *Organic Letters*, 20(18), 5877-5880.  
<https://doi.org/10.1021/acs.orglett.8b02543>

Peer reviewed version

Link to published version (if available):  
[10.1021/acs.orglett.8b02543](https://doi.org/10.1021/acs.orglett.8b02543)

[Link to publication record in Explore Bristol Research](#)  
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via ACS at <https://pubs.acs.org/doi/pdf/10.1021/acs.orglett.8b02543> . Please refer to any applicable terms of use of the publisher.

## University of Bristol - Explore Bristol Research

### General rights

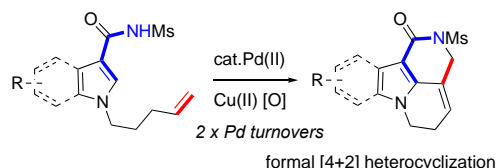
This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:  
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

# A Pd(II)-Catalyzed [4+2] Heterocyclization Sequence for Polyheterocycle Generation

Elizabeth L. Glaisyer, Michael S. Watt, Kevin I. Booker-Milburn\*

School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, U.K.

Supporting Information Placeholder



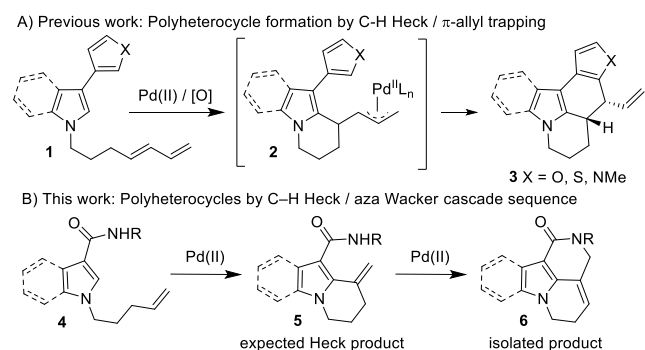
**ABSTRACT:** A new Pd(II)-catalyzed cascade sequence for the formation of polyheterocycles, from simple starting materials, is reported. The sequence is applicable to both indole and pyrrole substrates, and a range of substituents are tolerated. The reaction is thought to proceed by a Pd(II)-catalyzed C–H activated Heck reaction followed by a second Pd(II)-catalyzed aza-Wacker reaction with two Cu(II)-mediated Pd(0) turnovers per sequence. The sequence can be considered a formal [4+2] heterocyclization.

Polyheterocycles are commonly found in a wide range of molecules<sup>1</sup> as privileged structures in drug discovery,<sup>2</sup> in the cores of many natural products<sup>3</sup> and in synthetic dyes<sup>4</sup> and OLEDs.<sup>5</sup> It is important therefore that efficient new methodologies for the construction of such structures are developed to aid advances in medicines and materials. In recent years, there has been intense activity in the development of new transition metal catalyzed C–H activation reactions<sup>6</sup> due to their potential to reduce step count and waste generated by conventional cross-coupling reactions involving aryl halides. The use of such direct reactions in a cascade sequence allows complex drug- and natural product-like molecules to be constructed rapidly from simple starting materials.<sup>7</sup> We have previously shown that an indole or pyrrole core bearing an *N*-tethered diene **1** can, by way of Heck cyclization, be used to generate  $\pi$ -allyl intermediates such as **2**, which in turn can be trapped by a variety of internal heterocyclic nucleophiles (Scheme 1A).<sup>8</sup> This work was later extended by switching the heterocyclic nucleophile to an internal heteroatom nucleophile, forming diaza-heterocyclic systems.<sup>9</sup> Herein, we describe how complex polyheterocycles such as **6** can be assembled in one step from simple heterocyclic tethered *alkenes* by way of a novel C–H activated Heck / aza-Wacker sequence (Scheme 1B).

While investigating the first step of the mechanism involved with reaction of **1**, and related processes with dienes, we synthesized the simple alkenyl tethered indole carboxylate **4** (R = Ts). It was assumed that the straightforward oxidative Heck cyclized product **5** (R = Ts) would be obtained as no  $\pi$ -allyl intermediate would be formed (cf. **2**) and the reaction would therefore proceed

by  $\beta$ -hydride elimination to **5**. However, when **4** (R = Ts) was subjected to the cyclization conditions using 10 mol % Pd(OAc)<sub>2</sub> and 2.5 equivalents Cu(OAc)<sub>2</sub> as an oxidant the cascade product **6** (R = Ts) was observed in 25% yield. It was proposed that this was due to the putative Heck intermediate **5** (R = Ts) undergoing an adventitious Pd(II)-catalyzed aza-Wacker type reaction with the CONHTs group. Previous studies<sup>10</sup> have demonstrated cascade reactions of O-hydroxamic acid ethers under Rh(III) catalysis. Here, the preformed N–O bond served as an internal oxidant for the Rh(I) redox cycle. In our case, with Pd(II)/Cu(II), the formation of the cascade product **6** was a very surprising result and was therefore explored further as an attractive proposition for replacing synthetically demanding dienes with simple alkenes in these cascade processes.

## Scheme 1. Generation of complex polycyclic heterocycles via Pd(II)-catalyzed cascade sequences.<sup>8-9</sup>



Preliminary optimization studies (Table 1) saw an increase in yield from 25% to 50% on increasing the equivalence of  $K_2CO_3$  to 2.5 equivalents with both  $Pd(OAc)_2$  and  $Pd(TFA)_2$  (Table 1, entries 1-3). The tosylamide product **6a** proved to be insoluble in common laboratory solvents, hindering purification and analysis, and so a change in directing group (R) was investigated. The *N*-benzoyl amide substrate **4b** was surprisingly unreactive when subjected to the cyclization conditions and no product **6b** was observed (Table 1, entry 4). This result suggests that N–H pKa was an important factor and so the *N*-mesylamide **4c** was also evaluated, as this should have similar electronic properties to **4a**. Pleasingly, this performed equally well to the *N*-tosylamide **4a**, giving the much more soluble **6c** in 52% yield (Table 1, entry 4).

**Table 1. Preliminary optimization studies**

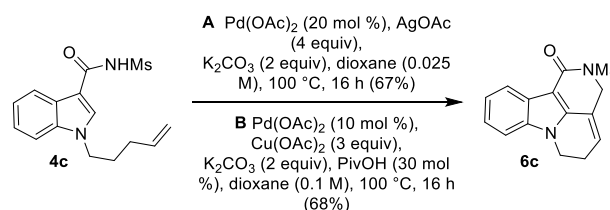
a, R = Ts; b, R = Bz; c, R = Ms

entry	catalyst	base equiv	product	yield (%)
1	$Pd(OAc)_2$	1	<b>6a</b>	25
2	$Pd(OAc)_2$	2.5	<b>6a</b>	50
3	$Pd(TFA)_2$	2.5	<b>6a</b>	50
4	$Pd(TFA)_2$	2.5	<b>6b</b>	0
5	$Pd(TFA)_2$	2.5	<b>6c</b>	52

Further optimization of this reaction by a traditional iterative approach proved frustrating, as yields remained at the 50% mark. We therefore embarked on a basic Design of Experiments (DoE) study to identify the optimum conditions. The use of DoE has become increasingly important over recent years due to its ability to derive expansive information on reaction conditions from a condensed subset of defined experiments.<sup>11</sup> Using MODDE software, 7 variables were chosen and (using a linear model) 22 experiments were run, including three centre points (see Supporting Information (SI) for detail). It was found that the type of catalyst used was the most significant factor, with  $Pd(OAc)_2$  giving the best results. It was also found that a higher temperature and a higher catalyst loading were beneficial, whereas a larger excess of base had a negative effect. The optimum conditions (**A**, Scheme 2) from the DoE study were as follows:  $Pd(OAc)_2$  (20 mol %), AgOAc (4 equivalents),  $K_2CO_3$  (2 equivalents). Unfortunately, these conditions have clear limitations, such as the high catalyst loading and large excess of expensive AgOAc oxidant required. There are many literature precedents from Yu on the use of mono *N*-protected amino acids<sup>12</sup> and other organic acids<sup>13</sup> as additives for C–H activation methodology. Inspired by this, an additional screen of organic acids was undertaken using the optimized DoE results, yielding further improvements in the experimental procedure. Although a number of acids yielded positive results (see SI), ultimately PivOH (30 mol %) was chosen as the most readily available of the additives. Equally importantly this allowed for a lower Pd loading (10 mol %) and use of 3 equivalents  $Cu(OAc)_2$  in place of AgOAc (Conditions **B**, Scheme 2).

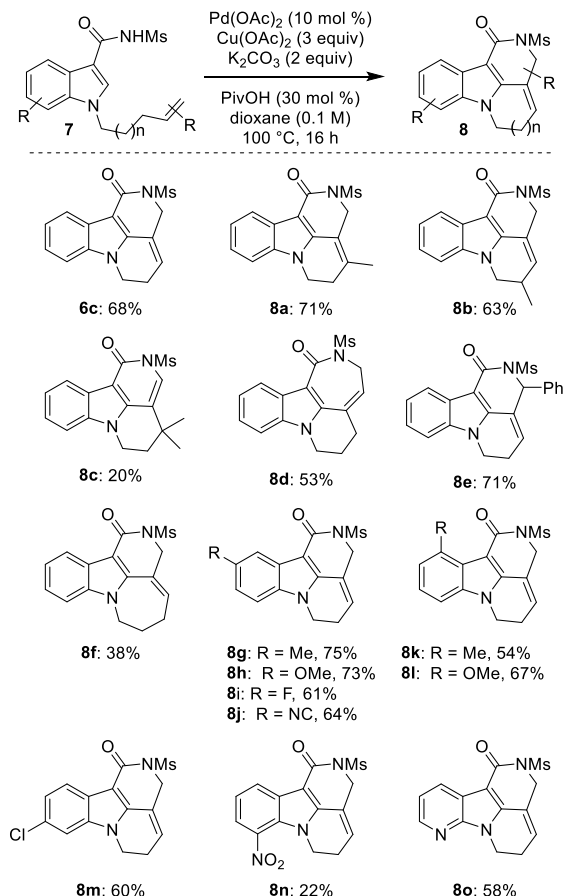
With these optimized conditions in hand, the scope of the reaction was investigated. Initially, we explored substitution of the alkene and carbon chain of the starting substrate (Scheme 3, **8a-f**). Chain branching was well tolerated, and gave the methyl isomers **8a,b** in similar yields to the parent compound. Conversely, gem-dimethyl substitution at the carbon adjacent to the alkene was significantly detrimental to the yield of **8c**. This could be a result of the change in direction of  $\beta$ -hydride elimination (see Scheme 5), or due to steric effects. A surprising result was observed when a methyl group was added to the terminal position of the alkene (**7d**), where instead of the usual [6,6] ring formation, the [6,7] product **8d** was observed (see Scheme 5).

**Scheme 2. Result of optimization studies using DoE and additives**



Phenyl substitution at the terminal alkene carbon gave the expected alkene product **8e** in good yield. For the cascade methodologies developed previously, extension of the chain to enable 7-membered ring formation proved unsuccessful.<sup>8-9</sup> It was pleasing therefore to observe the formation of **8f** in moderate yield.

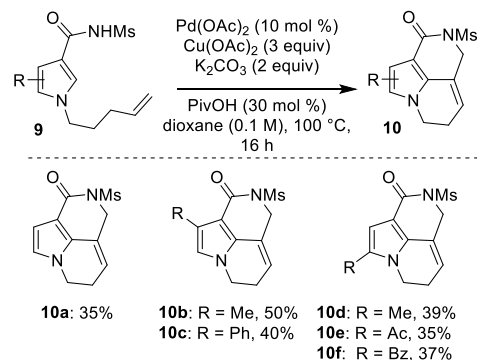
**Scheme 3. Pd(II)-catalyzed C–H activated Heck / aza-Wacker cascade reactions of indoles**



Substitution of the indole ring was also investigated (Scheme 3, examples **8g-o**). The reaction showed little preference for either electron-rich or electron-poor groups. For example, substituents at positions 4, 5 and 6 were all well tolerated (**8g-m**) and included halide (**8i,m**), nitrile (**8j**) and ether (**8h,l**) groups. Substitution at the 7-position was less successful (**8n**), although this was likely due to the high insolubility of the nitro substrate **7n**. It was expected that the 7-aza indole **7o** would perform poorly due to the basic pyridine nitrogen and its potential ability to act as a deactivating ligand, but pleasingly even this cascade sequence proceeded to give novel heterocycle **8o** in 58% yield.

The scope of this methodology was expanded further by switching from an indole substrate to a pyrrole substrate (Scheme 4). Unfortunately, the yields for these systems were less than that seen for indoles. It is thought that this is due to a lower catalytic turnover. We were however able to synthesize a range of such compounds and demonstrate the tolerance to substitution at both the 4 and 5 positions of the pyrrole ring (**9b-f**). Moderate yields were obtained for all pyrrole cyclizations, although these substrates/products all appeared to be more sensitive to decomposition under the reaction conditions.

**Scheme 4.** Pd(II)-catalyzed C–H activated Heck / aza-Wacker cascade reactions of pyrroles

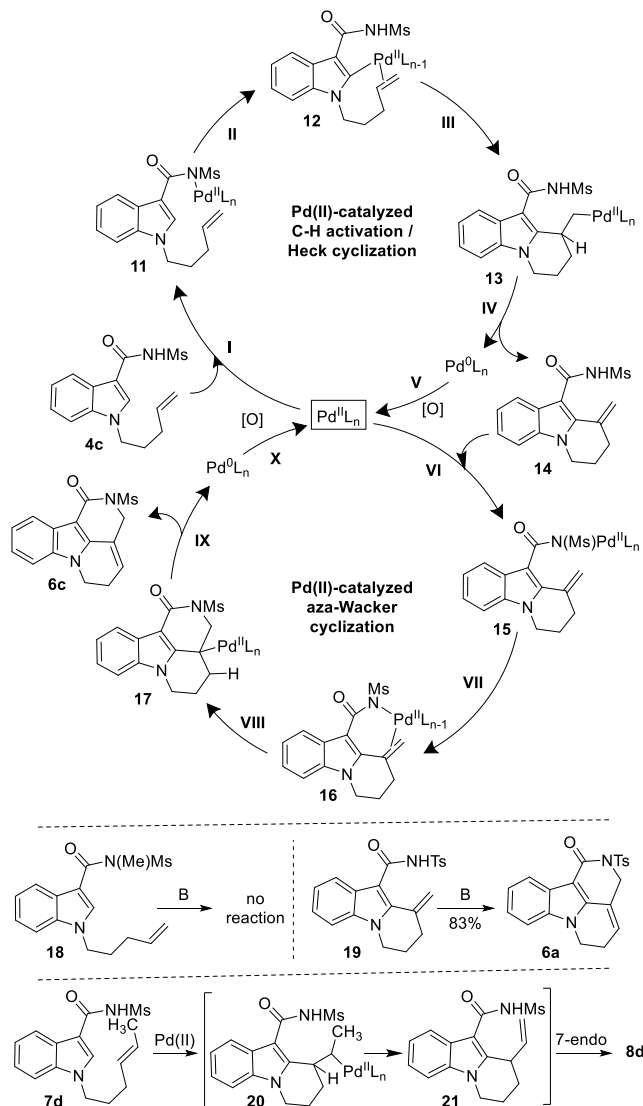


A plausible mechanistic description of this complex cascade is presented in Scheme 5. Initially, **4c** undergoes base catalyzed *N*-metalation<sup>16</sup> with  $\text{Pd}(\text{II})\text{L}_n$  (**I**), followed by directed C–H activation of the indole C2 (**II**).<sup>9</sup> Cyclization of **12** by carbometallation (**III**) followed by  $\beta$ -hydride elimination (**IV**) gives **14**. Redox with  $\text{Cu}(\text{II})$  then regenerates the active  $\text{Pd}(\text{II})\text{L}_n$  species (**V**). Intermediate **14** then enters the second catalytic cycle involving base catalyzed *N*-metalation (**VI**) and amino-palladation (**VII/VIII**) to **17**, which after  $\beta$ -hydride elimination (**IX**) gives product **6c** and  $\text{Pd}(\text{0})\text{L}_n$  which can enter a second redox cycle with  $\text{Cu}(\text{II})$ . Stahl<sup>14</sup> has undertaken a number of elegant studies supporting a *syn*-amino palladation mechanism for such aza-Wacker processes.

This double catalytic cycle is supported by a number of experimental observations. First, the reaction requires at least two equivalents of  $\text{Cu}(\text{II})$  oxidant, thus providing evidence of two palladium turnovers per cascade sequence. Further methylation of the *N*-mesylamide results in a substrate **18** that is inert to the reaction conditions (100% starting material recovered), indicating that the first step **I** involves metalation of the *N*-mesylamide. We were able to prepare the proposed intermediate **19** (as tosylamide – see SI) and when subjected to reaction conditions **B**, we obtained the product **6c** in 83% yield, thus strongly supporting its role as an intermediate in the cascade sequence. Finally, the interesting 7-membered ring formation when the methyl substrate **7d** was used is likely a result of the cyclized Pd-species **20** undergoing an entropically more favoured elimination to the terminal alkene **21** followed by a 7-*endo* aza-Wacker cyclization to **8d**.

In conclusion, we have developed a novel Pd(II)-catalyzed sequence for the rapid formation of polyheterocycles from simple substrates in a cascade procedure that can be considered a [4+2] heterocyclization. Evidence has been presented to suggest that the overall sequence proceeds by a C–H activated, oxidative Heck cyclization followed by an aza-Wacker cyclization. The reaction has been shown to be tolerant of a range of substitution on both the carbon chain and heterocyclic core and works for both substituted indoles and pyrroles.

**Scheme 5.** Proposed mechanism for C–H activated Heck / aza-Wacker sequence



Current work is underway to extend the methodology to non-aromatic scaffolds, which could serve as a key step toward the total synthesis of naturally-occurring alkaloids and potential drug discovery scaffolds.

## ASSOCIATED CONTENT

Experimental procedures and spectroscopic data. This material is available free of charge on the ACS Publications website at DOI: xxxxxx

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: k.booker-milburn@bristol.ac.uk

## ACKNOWLEDGMENTS

We thank the EPSRC Bristol Chemical Synthesis Doctoral Training Centre (EP/G036764/1) for PhD studentship funding to ELG and MSW.

## REFERENCES

- (a) Sravanthi, T. V.; Manju, S. L., *Eur. J. Pharm. Sci.* **2016**, *91*, 1-10; (b) Stefan, W.; S., B. R.; Kamal, K.; Herbert, W., *Angew. Chem. Int. Ed.* **2011**, *50*, 10800-10826.
- (a) Zai-Qun, L., *Mini Rev. Org. Chem.* **2016**, *13*, 166-183; (b) Martins, P.; Jesus, J.; Santos, S.; Raposo, L.; Roma-Rodrigues, C.; Baptista, P.; Fernandes, A., *Molecules* **2015**, *20*, 16852; (c) Vitaku, E.; Smith, D. T.; Njardarson, J. T., *J. Med. Chem.* **2014**, *57*, 10257-10274; (d) Antonino, L.; Alessio, T.; Carla, G.; Annamaria, M.; Giuseppe, G.; Giampaolo, B.; Anna Maria, A., *Lett. Drug Des. Discov.* **2014**, *11*, 15-26.
- (a) Hu, J.-F.; Fan, H.; Xiong, J.; Wu, S.-B., *Chem. Rev.* **2011**, *111*, 5465-5491; (b) Ishikura, M.; Yamada, K.; Abe, T., *Nat. Prod. Rep.* **2010**, *27*, 1630-1680; (c) Walker, S. R.; Carter, E. J.; Huff, B. C.; Morris, J. C., *Chem. Rev.* **2009**, *109*, 3080-3098; (d) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F., *Chem. Rev.* **2008**, *108*, 264-287; (e) Aloise Pilli, R.; da Conceicao Ferreira de Oliveira, M., *Nat. Prod. Rep.* **2000**, *17*, 117-127.
- Vasilev, A.; Deligeorgiev, T.; Gadjev, N.; Kaloyanova, S.; Vaquero, J. J.; Alvarez-Builla, J.; Baeza, A. G., *Dyes Pigm.* **2008**, *77*, 550-555.
- (a) Facchetti, A., *Chem. Mater.* **2011**, *23*, 733-758; (b) Su, S.-J.; Cai, C.; Kido, J., *Chem. Mater.* **2011**, *23*, 274-284.
- (a) Kou, X.; Shao, Q.; Ye, C.; Yang, G.; Zhang, W., *J. Am. Chem. Soc.* **2018**, *140*, 7587-7597; (b) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J., *Chem. Soc. Rev.* **2016**, *45*, 2900-2936; (c) Chen, C.; Hecht, M. B.; Kavara, A.; Brennessel, W. W.; Mercado, B. Q.; Weix, D. J.; Holland, P. L., *J. Am. Chem. Soc.* **2015**, *137*, 13244-13247; (d) Yasutomo, S.; Takehisa, M.; Kenichiro, I., *Angew. Chem. Int. Ed.* **2015**, *54*, 66-81; (e) Wencel-Delord, J.; Glorius, F., *Nat. Chem.* **2013**, *5*, 369; (f) McDonald, R. I.; Liu, G.; Stahl, S. S., *Chem. Rev.* **2011**, *111*, 2981-3019; (g) Lyons, T. W.; Sanford, M. S., *Chem. Rev.* **2010**, *110*, 1147-1169; (h) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q., *Angew. Chem. Int. Ed.* **2009**, *48*, 5094-5115; (i) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S., *Chem. Rev.* **2007**, *107*, 5318-5365; (j) Labinger, J. A.; Bercaw, J. E., *Nature* **2002**, *417*, 507.
- (a) Lv, N.; Chen, Z.; Liu, Y.; Liu, Z.; Zhang, Y., *Org. Lett.* **2017**, *19*, 2588-2591; (b) Bai, P.; Huang, X.-F.; Xu, G.-D.; Huang, Z.-Z., *Org. Lett.* **2016**, *18*, 3058-3061; (c) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I., *J. Am. Chem. Soc.* **2008**, *130*, 10066-10067; (d) Abbiati, G.; Beccalli, E.; Broggini, G.; Martinelli, M.; Paladino, G., *Synlett* **2006**, 0073-0076.
- Cooper, S. P.; Booker-Milburn, K. I., *Angew. Chem.* **2015**, *127*, 6596-6600.
- Watt, M. S.; Booker-Milburn, K. I., *Org. Lett.* **2016**, *18*, 5716-5719.
- (a) Baihua, Y.; A., D. P.; Nicolai, C., *Angew. Chem. Int. Ed.* **2014**, *53*, 507-511; (b) Shi, Z.; Bouladakis-Arapinis, M.; Koester, D. C.; Glorius, F., *Chem. Commun.* **2014**, *50*, 2650-2652; (c) Davis, T. A.; Hyster, T. K.; Rovis, T., *Angew. Chem. Int. Ed.* **2013**, *52*, 14181-14185.
- (a) Murray, P. M.; Bellany, F.; Benhamou, L.; Bucar, D.-K.; Tabor, A. B.; Sheppard, T. D., *Org. Biomol. Chem.* **2016**, *14*, 2373-2384; (b) Stone, S.; Wang, T.; Liang, J.; Cochran, J.; Green, J.; Gu, W., *Org. Biomol. Chem.* **2015**, *13*, 10471-10476; (c) Weissman, S. A.; Anderson, N. G., *Org. Process Res. Dev.* **2015**, *19*, 1605-1633.
- (a) Yang, Y.-F.; Hong, X.; Yu, J.-Q.; Houk, K. N., *Acc. Chem. Res.* **2017**, *50*, 2853-2860; (b) Plata, R. E.; Hill, D. E.; Haines, B. E.; Musaev, D. G.; Chu, L.; Hickey, D. P.; Sigman, M. S.; Yu, J.-Q.; Blackmond, D. G., *J. Am. Chem. Soc.* **2017**, *139*, 9238-9245; (c) Li, G.; Leow, D.; Wan, L.; Yu, J.-Q., *Angew. Chem. Int. Ed.* **2013**, *52*, 1245-1247; (d) Li, G.; Leow, D.; Wan, L.; Yu, J. Q., *Angew. Chem. Int. Ed.* **2013**, *52*, 1245-1247; (e) Engle, K. M.;

Wang, D.-H.; Yu, J.-Q., *J. Am. Chem. Soc.* **2010**, *132*, 14137-14151.

13. Lafrance, M.; Fagnou, K., *J. Am. Chem. Soc.* **2006**, *128*, 16496-16497.

14. (a) Ye, X.; Liu, G.; Popp, B. V.; Stahl, S. S., *J. Org. Chem.* **2011**, *76*, 1031-1044; (b) McDonald, R. I.; White, P. B.; Weinstein, A. B.; Tam, C. P.; Stahl, S. S., *Org. Lett.* **2011**, *13*, 2830-2833; (c) Liu, G.; Stahl, S. S., *J. Am. Chem. Soc.* **2007**, *129*, 6328-6335.

---